Chemistry 17: Section Handout 10

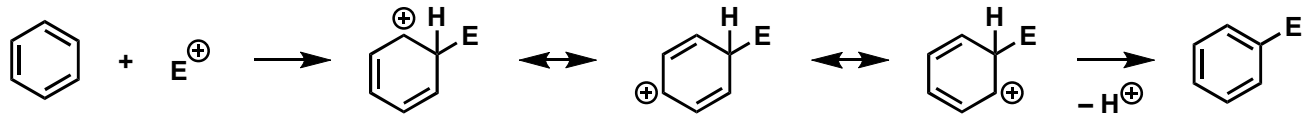
Topics: *electrophilic aromatic substitution, enols and enol equivalents, tautomerization mechanisms, regioselectivity under thermodynamic or kinetic control*

Key Concept Review

Electrophilic Aromatic Substitution (EAS): A class of reactions in which an aromatic ring acts as a nucleophile, resulting in the net substitution of a hydrogen atom on the ring with an electrophile.

Mechanism: EAS reactions all proceed by same basic mechanism**.** 1) A strong electrophile adds to an aromatic ring, breaking aromaticity; formation of this cationic, nonaromatic intermediate is the rate-determining step. 2) The cationic intermediate is deprotonated (at the carbon where the electrophile addition occurred) to restore aromaticity.

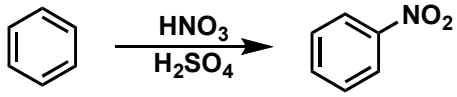
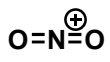
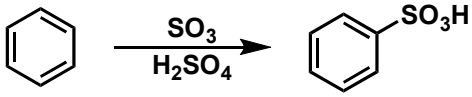
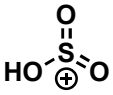
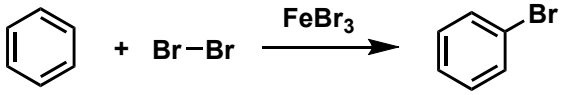
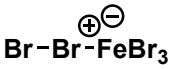
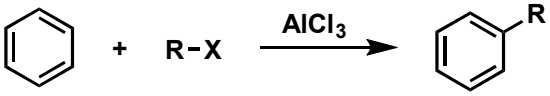
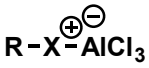
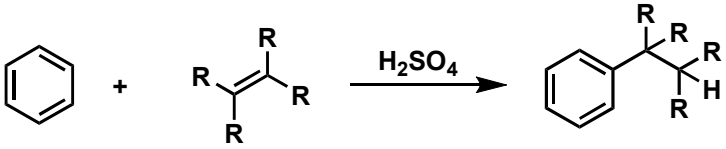
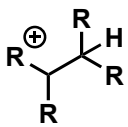
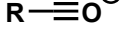
The positive charge in the cationic intermediates is delocalized over the ortho and para positions.



Step 1: *Electrophile Addition*

Step 2: *Deprotonation/Rearomatization*

Common electrophiles: Strong electrophiles are required for electrophilic aromatic substitution.

Reaction Class	*Transformation*	*Active Electrophile*
Nitration		
Sulfonation		
Bromination		
Friedel-Crafts Alkylation (Method 1)		
Friedel-Crafts Alkylation (Method 2)		
Friedel-Crafts Acylation		

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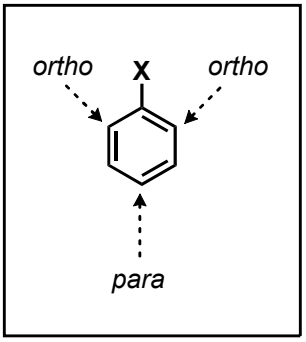
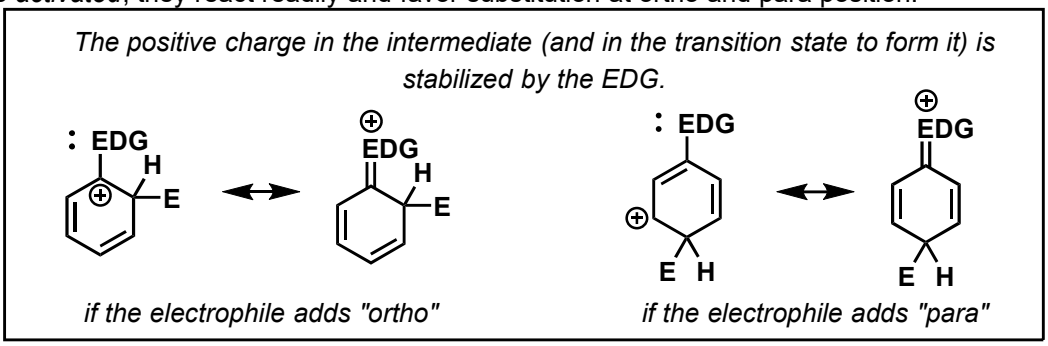
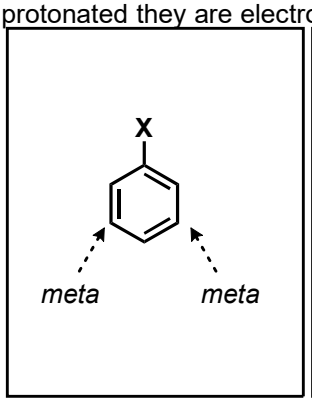
Regioselectivity of EAS: The substituents on the aromatic ring affect the regioselectivity of the EAS. There are two general classes of substituents: *electron-donating groups* (EDGs) and *electron-withdrawing groups* (EWGs). The strongest EDG or EWG on a ring dominates control of regioselectivity.

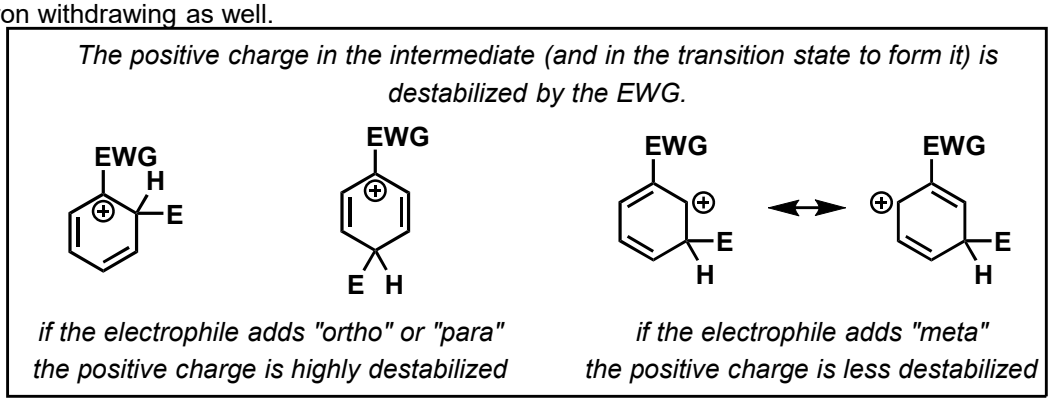
Typical EDGs include: alkyl groups, –OR, and $–NR_2$. Look for lone pairs that can be donated! Aromatic rings substituted with EDGs are *activated*; they react readily and favor substitution at ortho and para position.





Typical EWDs include: carbonyl groups, $–NO_2$ and –CN. Aromatic rings substituted with EWG's are *deactivated*; they react slowly and favor substitution at meta position. Keep an eye out for amines in acidic conditions- when protonated they are electron withdrawing as well.

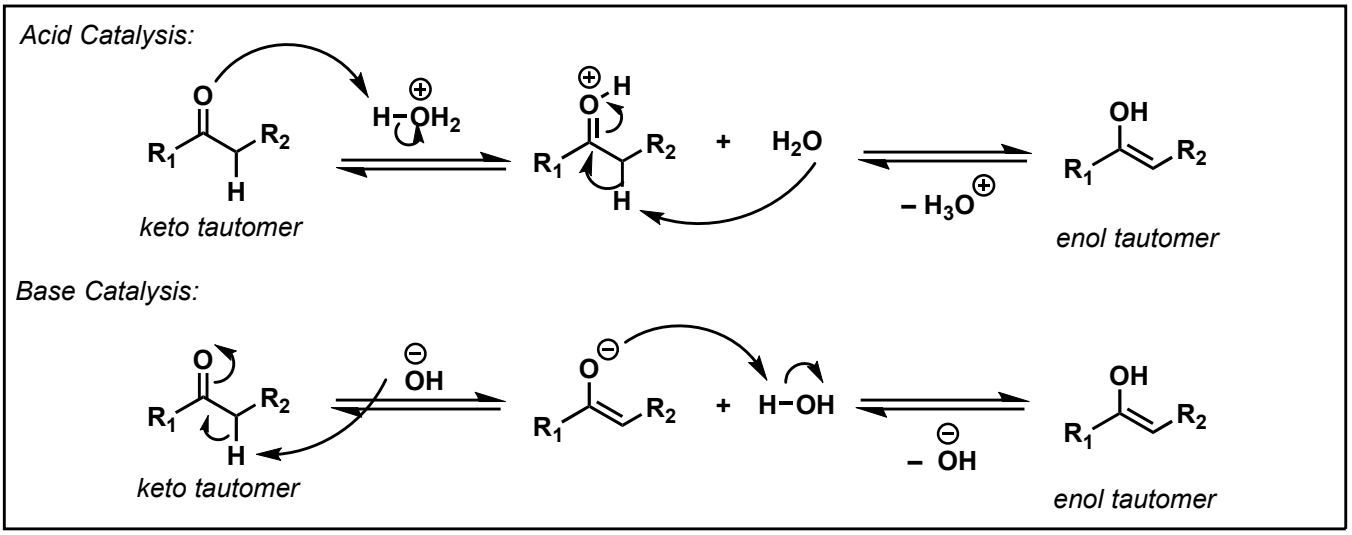




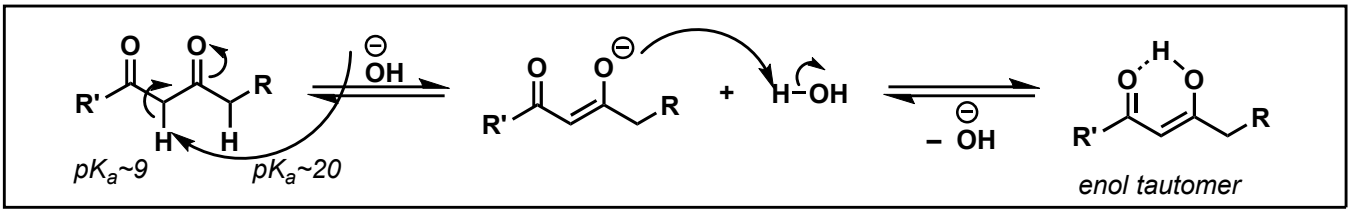
Halides are unusual because they are deactivating but ortho/para-directing due to their σ-withdrawing and weakly π-donating character.

Enol Equivalents and Tautomerism: Enols are structural isomers of carbonyl compounds (usually aldehydes or ketones), formed by a *tautomerization* mechanism, in which a proton is moved from the α-carbon to the carbonyl oxygen. While the "keto" tautomer of a carbonyl compound is more stable than the enol tautomer due to the strength of the C=O bond, the two forms exist in equilibrium in solution. Conversion between the two can be catalyzed by acid or base.

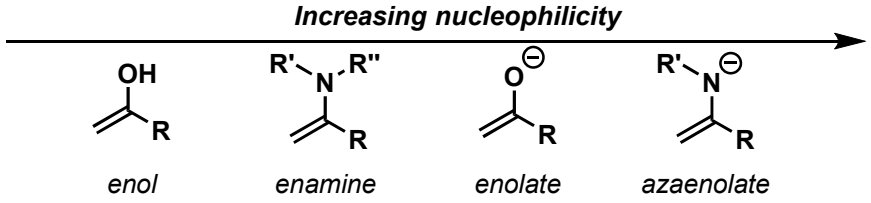
Keto/enol tautomerization



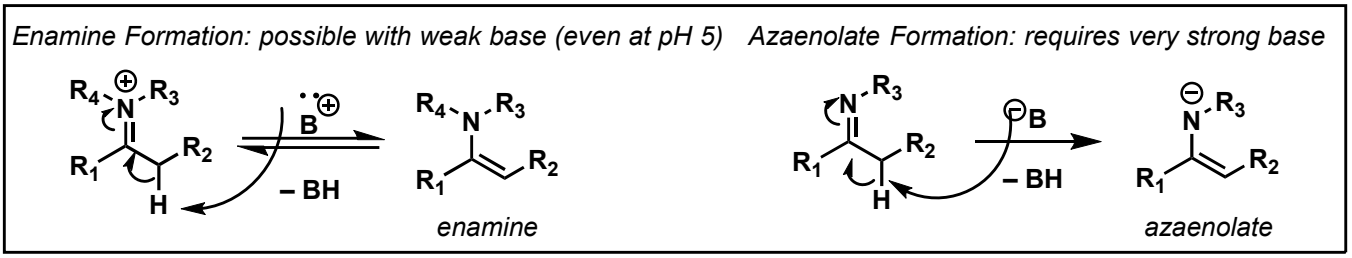
Tautomerism of β-dicarbonyl compounds: While keto-enol tautomerization normally favors the keto form, β-dicarbonyl compounds form stable enol tautomers due to the resulting extended conjugation and intramolecular hydrogen bond. As such, the proton at the α-carbon between the two carbonyl groups is unusually acidic.



Enol equivalents: While the keto tautomer of carbonyl compounds is electrophilic, the enol tautomer is relatively nucleophilic. Enols themselves are weak nucleophiles, but related compounds display a range of nucleophile strengths (and open up the possibility for interesting reactivity).

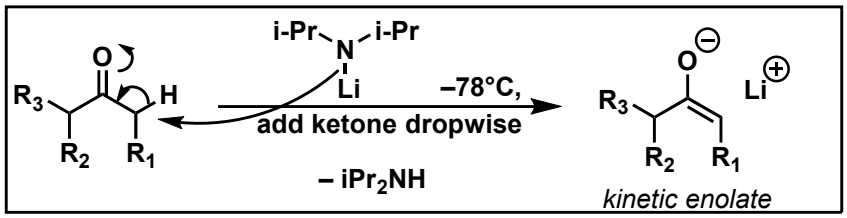


We briefly discussed the formation of enamines from iminium ions in Section 6. Similarly, azaenolates are formed by deprotonation of imines, but a much stronger base is required to accomplish this deprotonation.



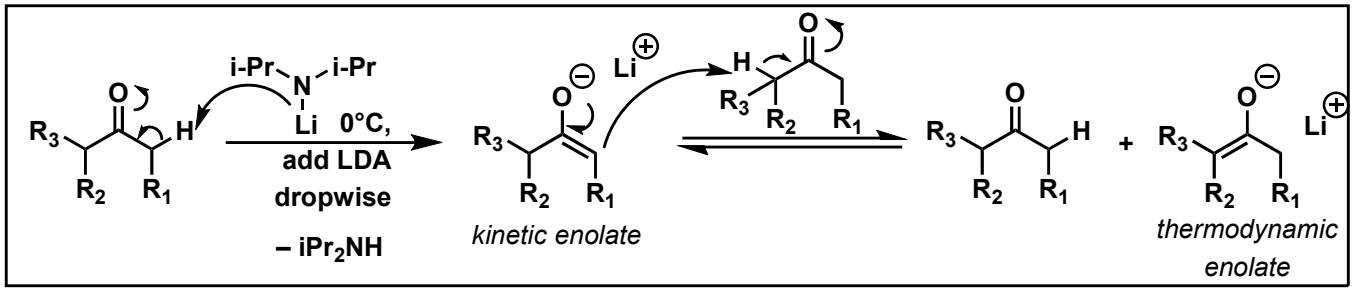
Kinetic vs. thermodynamic enolates: Enolates exist in equilibrium with the keto and enol tautomers in basic solution (see above), but they can also be generated quantitatively with stronger base. Depending on the precise conditions employed, enolates may often be generated regioselectively.

Kinetic Control: If the ketone is added to strong base at low temperature, the deprotonation will be under kinetic control. The deprotonation will occur at the least hindered site, generating the less-substituted enolate.



Note:
Lithium diisopropylamide (LDA) is commonly used to form enolates because it is strongly basic (pKa_H ~ 35) but poorly nucleophilic (due to its large bulk).

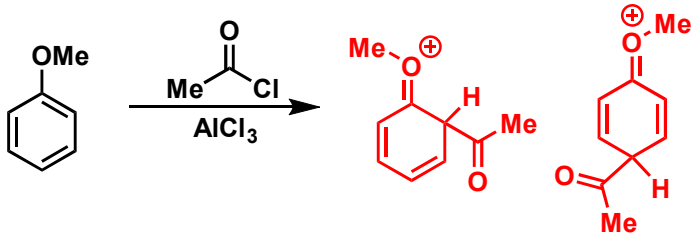
Thermodynamic Control: If strong base is added to ketone at moderate temperature, the deprotonation will be under thermodynamic control. After the kinetic enolate is generated, it can deprotonate the remaining ketone reversibly, generating the more-substituted, more-stable enolate.

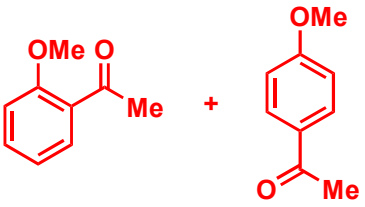


Workshop Problems

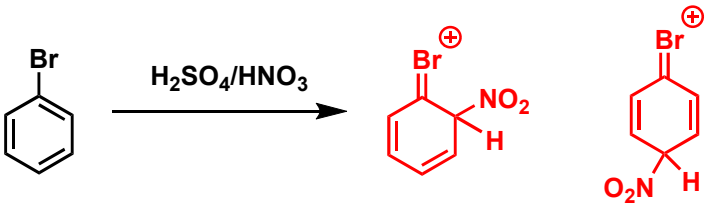
Workshop Problem 1: For each electrophilic aromatic substitution reaction shown below, predict which regio- and stereoisomer(s) of the indicated product are likely to form. Draw major resonance contributors of the carbocation intermediate to justify your product(s) structure(s).

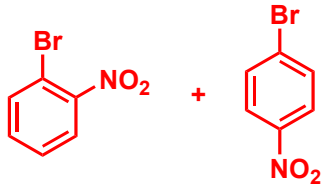
1-a.



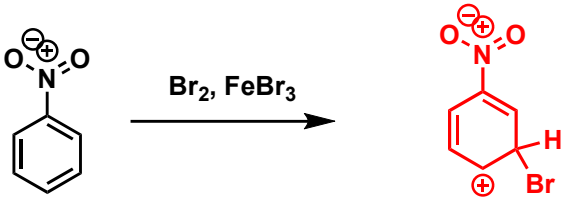


1-b.

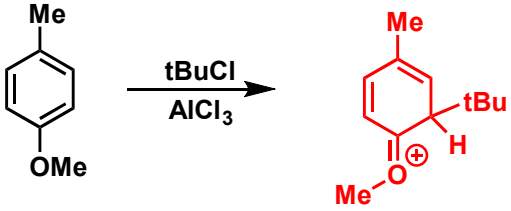


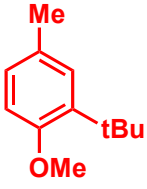


1-c.



1-d.





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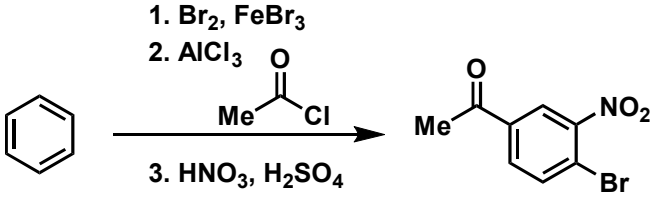
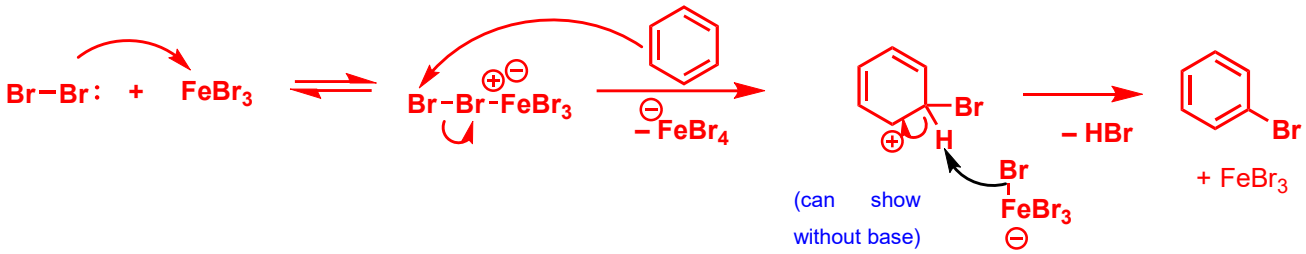
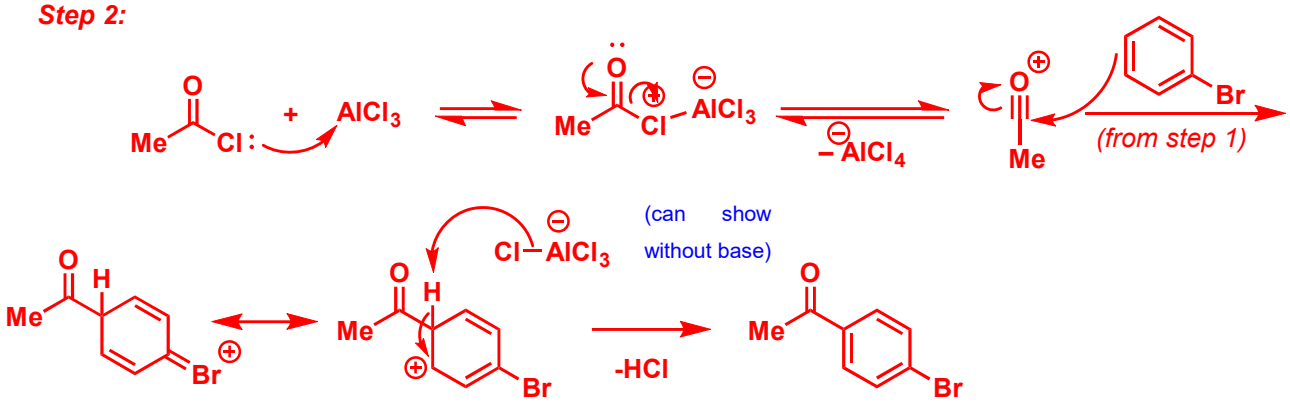
Workshop Problem 2: Electrophilic aromatic substitution reactions are often used in sequence to generate highly functionalized aromatic rings for use in pharmaceuticals, dyes, explosives, and semiconductors. Propose a mechanism for the conversion of benzene to the functionalized product shown below, using curved arrows to depict the redistribution of electrons in each step. For each carbocationic intermediate, draw the major resonance contributor. (You do not need to show the mechanism for the formation of the electrophile for the nitration step, but should start with the structure of the active electrophile).



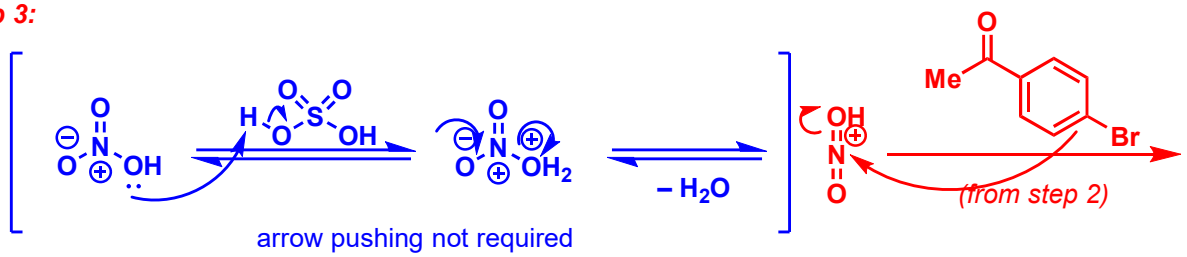
Step 1:



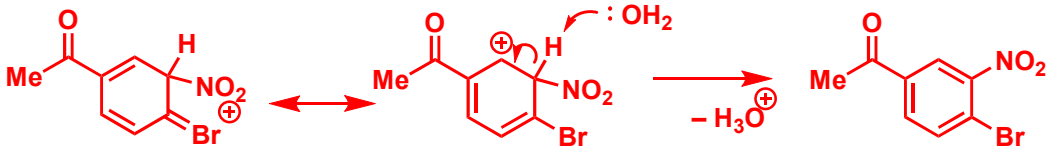
Step 2:



Step 3:



also accept deprotonation w HSO_4^- since water isn't explicit, or no base at all!



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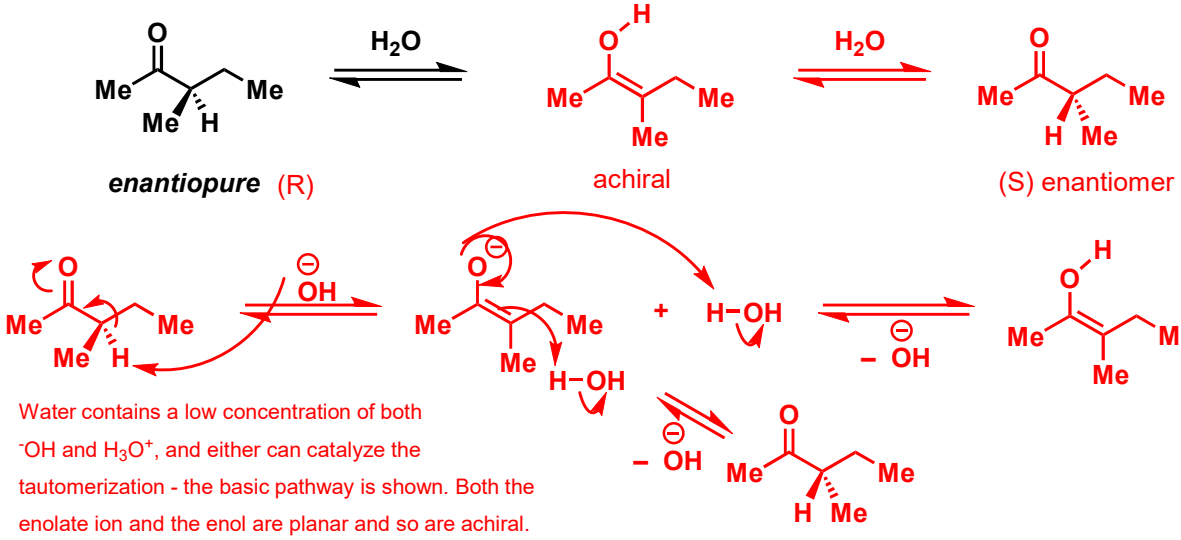
Workshop Problem 3: Provide a brief explanation for each of the following experimental observations. Use structural drawings, mechanisms and/or words.

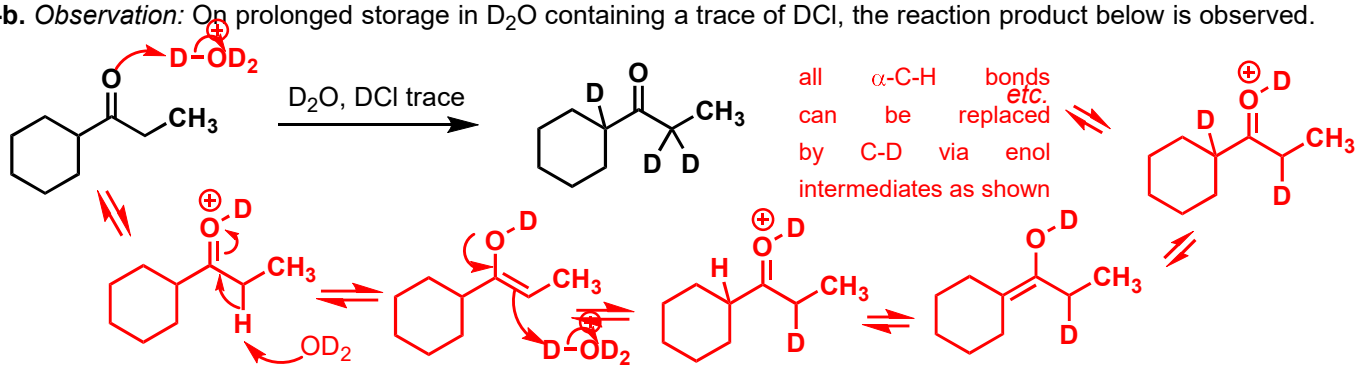
3-a. *Observation:* When an enantiopure sample of the ketone below is dissolved in water, the optical activity of the solution gradually diminishes to zero. Suggest a mechanism that explains this observation. [Recall that optical activity is a property of enantiopure compounds, or mixtures which contain an excess of one enantiomer.]



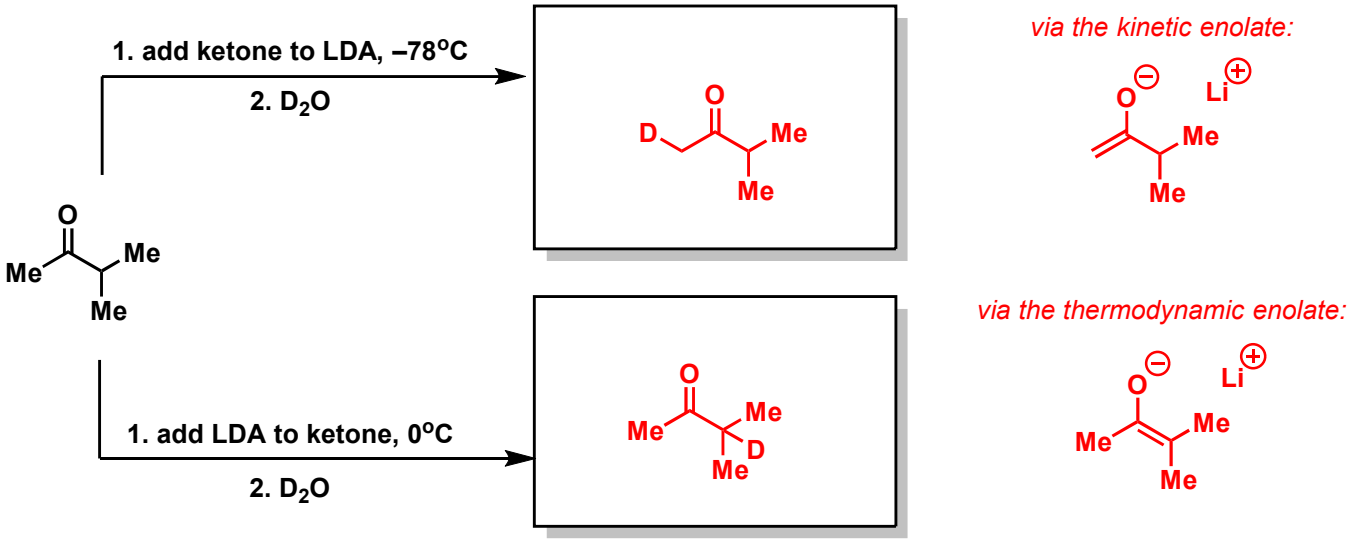
Water contains a low concentration of both ^{-}OH and H_3O^{+}, and either can catalyze the tautomerization - the basic pathway is shown. Both the enolate ion and the enol are planar and so are achiral.

Protonation of the planar enolate on the opposite face leads to production of the other enantiomer. Over time a racemic mixture of the 2 enantiomers will form as they are of equal energy as well as some of the achiral enol and so the solution loses its optical activity.

3-b. *Observation:* On prolonged storage in D_2O containing a trace of DCl, the reaction product below is observed.

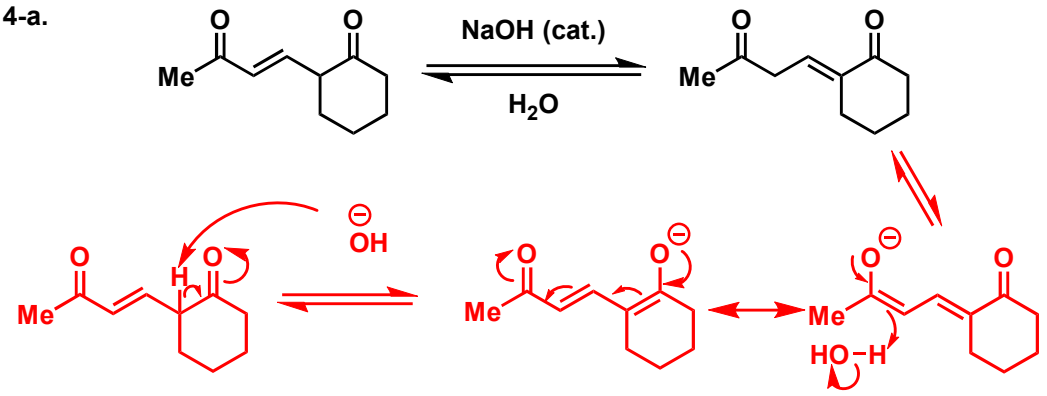


3-c. *Observation:* The ketone below is deprotonated quantitatively, then quenched with D_2O, to incorporate a single deuterium atom in the product. Depending on the deprotonation conditions, the site of deuterium incoporation differs. As part of your explanation, suggest a structure for the product under each set of conditions.

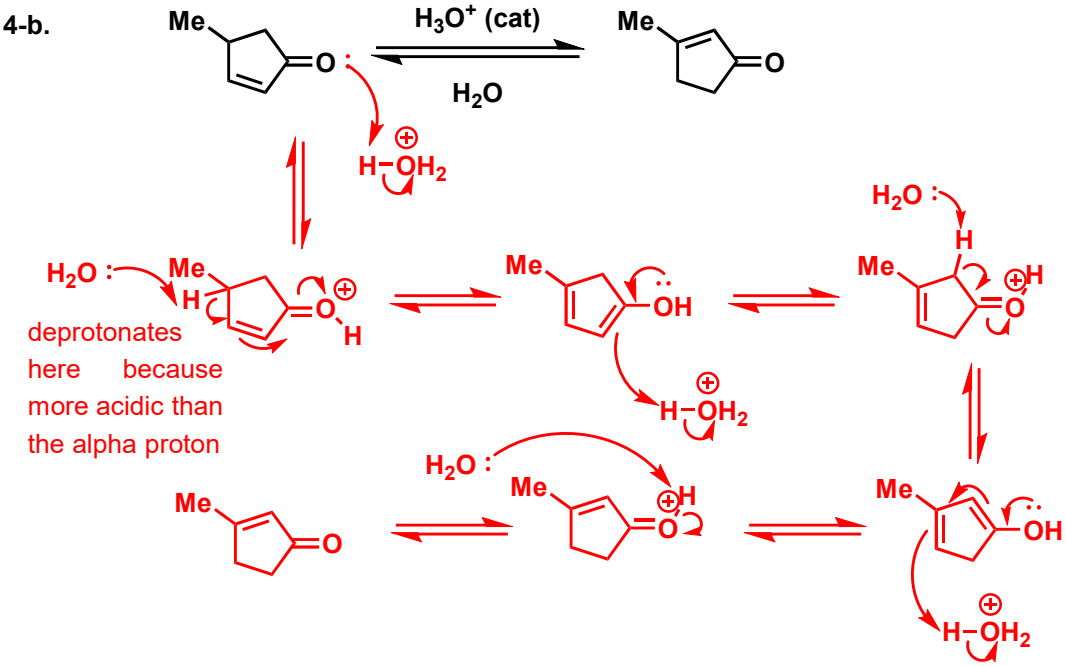


Workshop Problem 4: The following reactions involve keto-enol tautomerization. Propose a curved arrow mechanism for each reaction.

4-a.



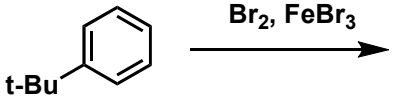
4-b.



Skillbuilder Problem 1: Regioselectivity of Electrophilic Aromatic Substitution Reactions

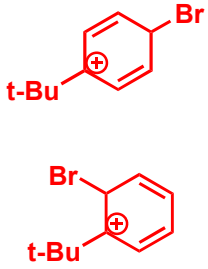
For each electrophilic aromatic substitution reaction shown below, predict which regioisomers of product are likely to form. Unless an excess of reagent is indicated, you only need to consider monosubstitution products. Draw the **major** resonance structure of any carbocation intermediate.

1-a.

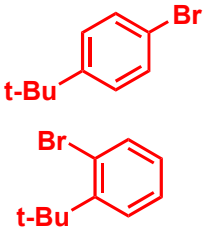


electrophile

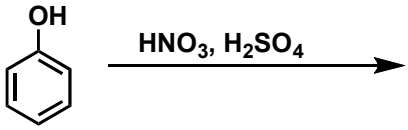
carbocations



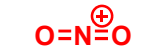
products



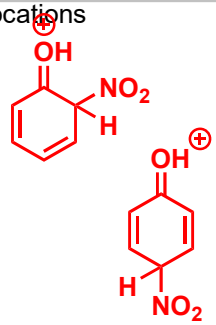
1-b.



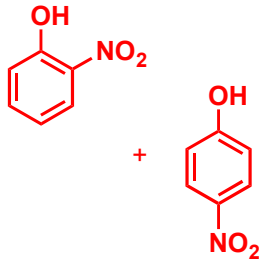
electrophile



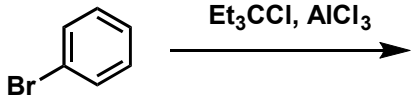
carbocations



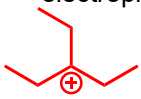
products



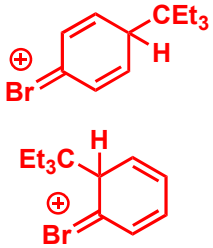
1-c.



electrophile



carbocations



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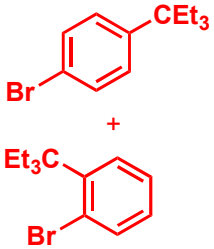

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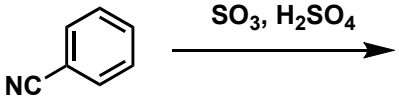

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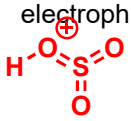

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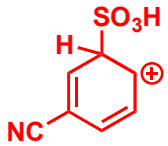
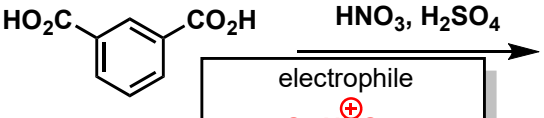


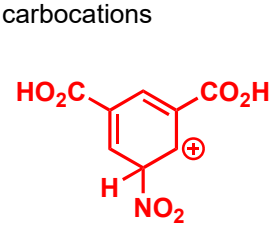
products

1-f.



electrophile

carbocations



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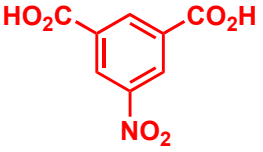
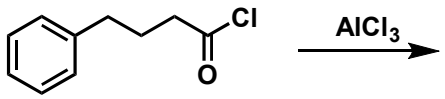
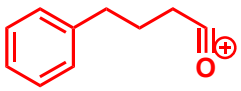


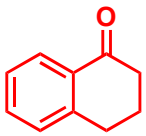
1-g.



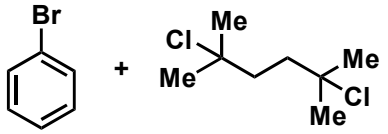
electrophile



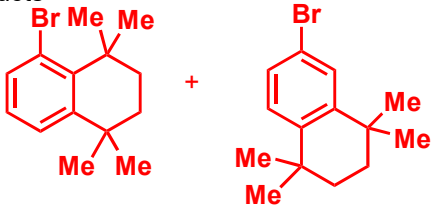
products



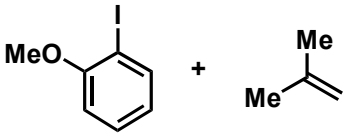
1-h.



products



1-i.



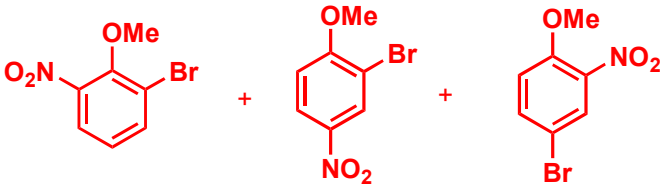
electrophile

products

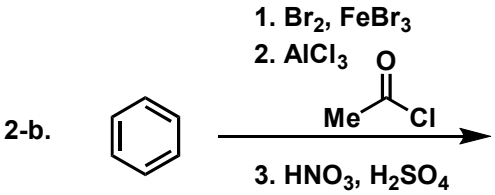
Skillbuilder problem 2: Draw the major possible regioisomers of the products of the following reaction sequences, using the number of possib le products as your guide.

2-a.

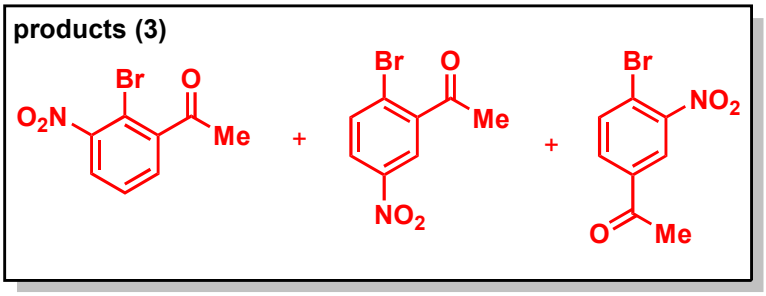
products (3)



2-b.

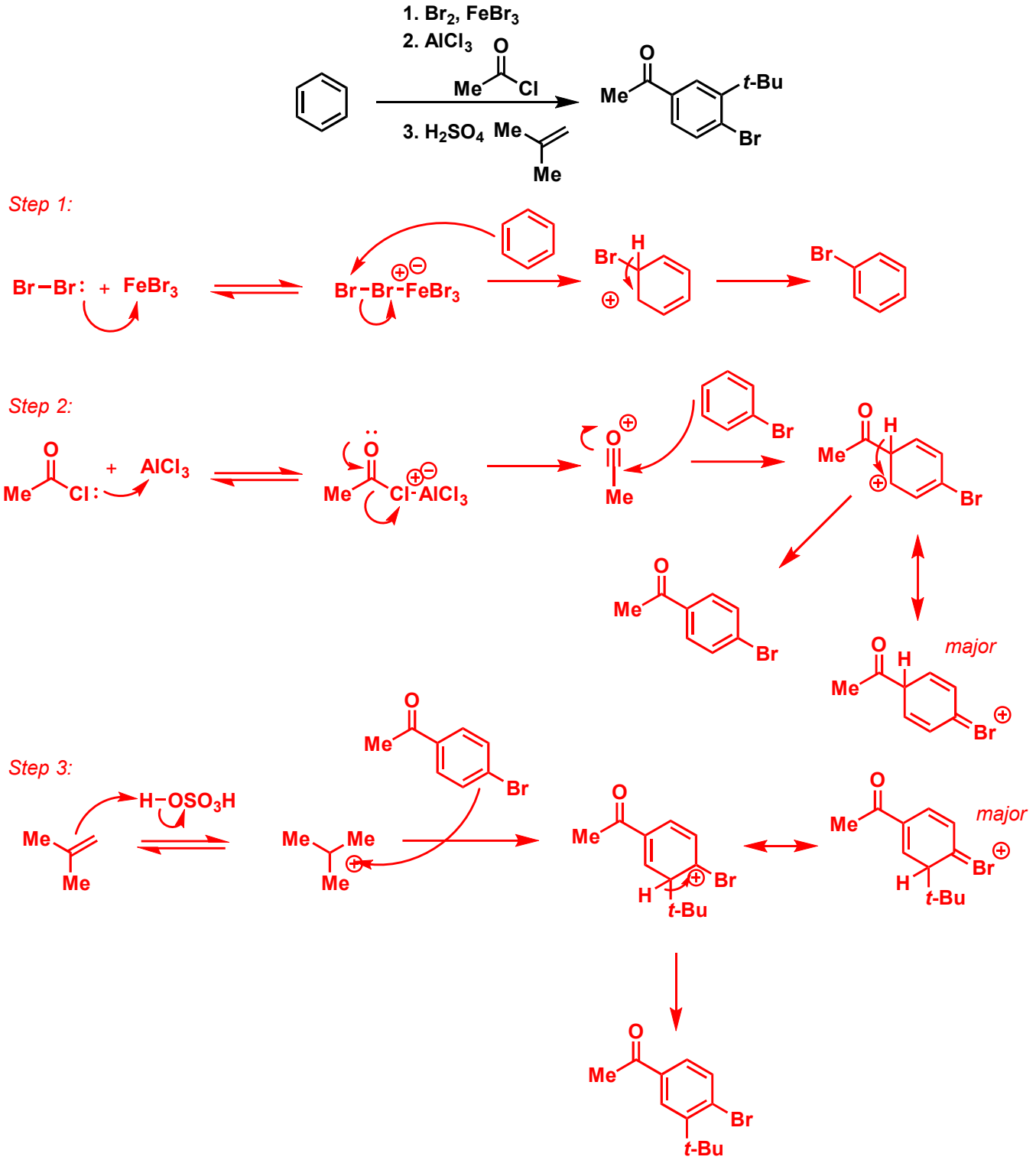


products (3)



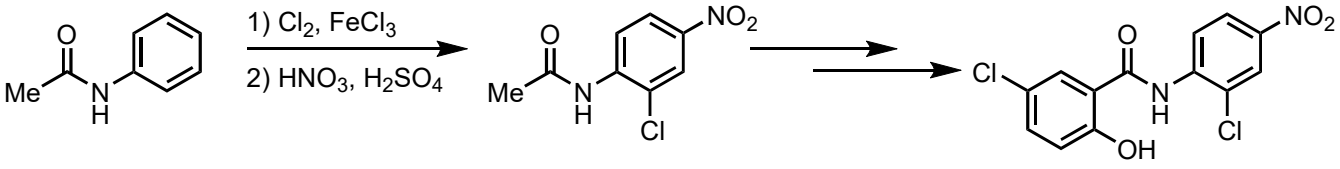
Challenge Problem 1: Mechanism of Electrophilic Aromatic Substitution Reactions

Propose a curved arrow mechanism for all steps of the reaction sequence shown below. Be sure to draw the major resonance structure of any carbocation intermediate as part of your mechanism.



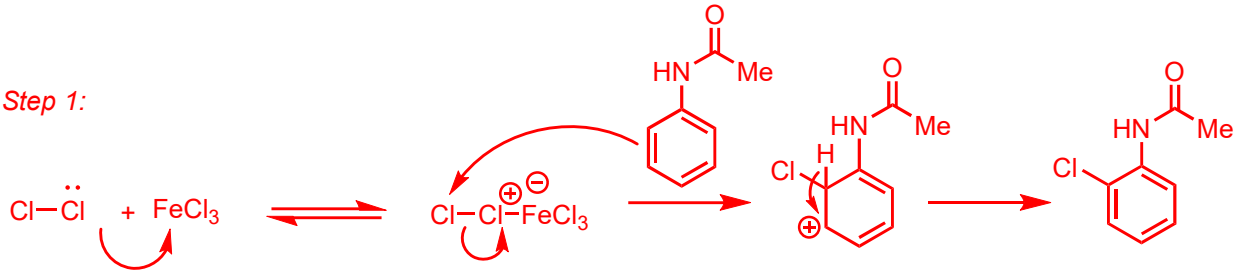
Challenge Problem 2:

2-a. 2-Chloro-4-nitroacetanilide can be used in the preparation of niclosamide, a medication used to treat tapeworm infections that appears on the World Health Organization's List of Essential Medicines. Propose a mechanism for the formation of 2-chloro-4-nitroaniline from acetanilide. You do not have to draw the mechanisms for formation of the active electrophilic species, but you must draw their structures. *Hint: The mechanism for aromatic chlorination is directly analogous to the mechanism for aromatic bromination.*

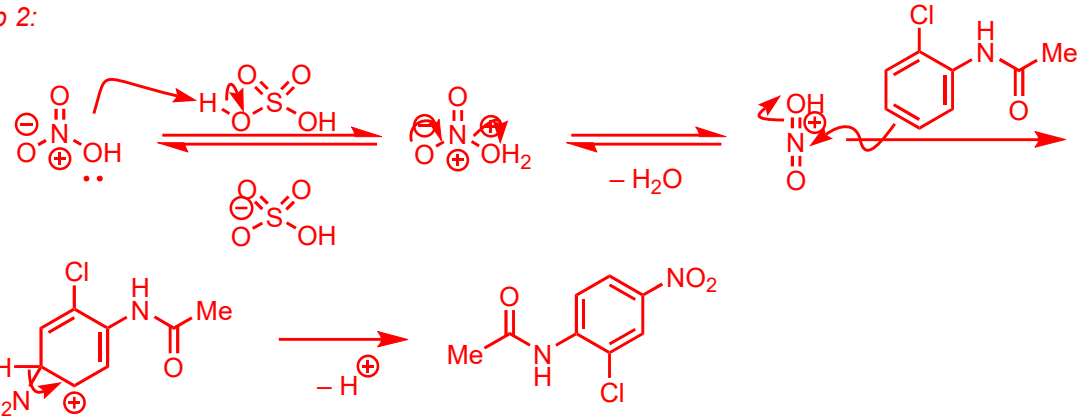


acetanilide 2-chloro-4-nitroacetanilide niclosamide

Step 1:

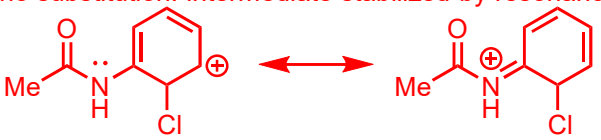


Step 2:

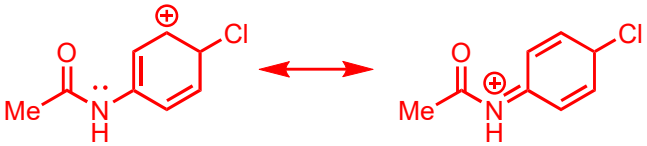


2-b. The first step of the reaction above produces a mixture of ortho and para-chlorinated products. Explain the reason for this regioselectivity using clearly drawn resonance structures.

Ortho substitution: intermediate stabilized by resonance



Para substitution: intermediate stabilized by resonance



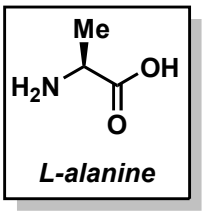
2-c. Consider the outcome of the reaction if the steps were performed in reverse order as follows: 1) HNO_3, H_2SO_4, 2) Cl_2, $FeCl_3$. Would 2-chloro-4-nitroacetanilide still be formed in this reaction? How would this change affect the rate of the chlorination step?

The regioselectivity of the chlorination step would not change (the amide directs to the ortho position and the nitro group directs to the meta position). However, the rate of the chlorination step would be slower because the nitro group deactivates the ring towards electrophilic aromatic substitution.

Challenge Problem 3:

Explain this observation: Even under acidic or basic conditions, solutions of L-alanine remain optically active.

As described in 3-a, keto-enol tautomerism would be expected to cause racemization of a stereocenter next to a carbonyl group.



Under acidic conditions, protonation of the amino group disfavors protonation of the carbonyl oxygen by an electrostatic effect, and thereby disfavors tautomerization.The first step of acid-catalyzed tautomerization is carbonyl protonation.

Under basic conditions, formation of the carboxylate anion disfavors deprotonation at the alpha position and thereby disfavors tautomerization